

Breast cancer incidence and mortality before and after implementation of the German mammography screening program

Alexander Katalinic^{1,2}, Nora Eisemann¹, Klaus Kraywinkel³, Maria R. Noftz¹ and Joachim Hübner¹

¹Institute for Social Medicine and Epidemiology, University of Lübeck, Lübeck, Germany

²Institute for Cancer Epidemiology, University of Lübeck, Lübeck, Germany

³Department for Epidemiology and Health Reporting, German Centre for Cancer Registry Data, Robert Koch-Institute, Berlin, Germany

Effective population-based mammography screening should impact breast cancer (BC) incidence, age and stage-specific incidence and BC mortality. We aim to investigate such effects in a time period of 10 years after implementation of the German mammography screening program. Data on 323,719 breast cancer patients from 2003 to 2014 for defined regions covering a population of 30 million inhabitants and official mortality data from 1998 to 2016 for almost the whole of Germany were used. We compared incidence and mortality rates for the prescreening time period (2003/2004) and the latest available data (2013/2014 and 2015/2016, respectively) and performed trend analyses using joinpoint regression models. In the screening exposed age groups (50–59 and 60–69 years), BC incidence showed a typical prevalence peak with the introduction of the mammography screening, mainly driven by an increase of early-stage BC. For Stage III and IV BC incidence in 2013/2014 was 24.2 and 23.0% (age group 50–59 years) and 28.3 and 24.2% (age group 60–69 years) lower than in the prescreening period. From 2003/2004 to 2015/2016 BC mortality decreased by 25.8 and 21.2%, respectively. As corresponding trends in nonexposed age groups were distinctly unfavorable, the reduction of late-stage BC incidence and BC mortality in the screening exposed age groups in Germany is most likely to be attributed to the introduction of the national mammography screening program. These positive effects are bought at the cost of a moderate occurrence of overdiagnosis, especially by a sharp increase of *in situ* cancers.

Introduction

Breast cancer (BC) is the most common cancer and the most common cancer-related cause of death in women in Germany. In 2018, about 72,000 incident cases were expected¹ and about

Key words: breast cancer, incidence, mortality, mammography screening

Abbreviations: APC: annual percentage change; BC: breast cancer; BIC: Bayesian information criterion; DCIS: ductal carcinoma *in situ*; DCO: death certificate only; EUREF: European Reference Organization for Quality Assured Breast Screening and Diagnostic Services; ICD10: International Classification of Diseases, 10th Revision; RCT: randomized controlled trial; UICC: Union for International Cancer Control

Conflict of interest: All authors declare no conflicts of interest.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

DOI: 10.1002/ijc.32767

History: Received 15 Aug 2019; Accepted 18 Oct 2019; Online 1 Nov 2019

Correspondence to: Prof. Dr. Alexander Katalinic, E-mail: alexander.katalinic@uksh.de

19,000 women died from BC in 2016.² To reduce the burden of BC in Germany a public debate about the implementation of an organized mammography screening started in the 1990s. Initial pilot projects were implemented in 2001. In 2002, the German parliament decided to introduce an organized, population-based national breast cancer screening program for women aged 50–69 years. In 2005, the rollout of the screening program, which is strictly following the European guidelines on breast cancer screening (EUREF),³ started and was completely implemented nation-wide until 2009. Key features of the program are: 94 mammography units (each covering a population of about 500,000 to 1 million), a centralized population-based invitation system, invitation every 2 years with a proposal of time and place for the examination, independent double reading of mammograms, high level quality assurance by reference centers and a national evaluation unit with yearly benchmarking. Today almost 100% of German women aged 50 to 69 years are invited to the mammography screening every 2 years, and participation rate is about 50% since the year 2009.⁴ The program is in full compliance with relevant quality process indicators of the EUREF guideline.

Until today, there is only a little information on population-based outcome measures of the German mammography screening like the frequency of advanced cancers or BC mortality.

What's new?

Effective mammography screening should have an impact on breast cancer (BC) incidence and mortality. Until today, however, there is little information available on the population-based outcomes of the national breast cancer screening program in Germany. Here, the authors present age-specific population-based data before and after implementation of the program. Compared to non-exposed age groups, screening-eligible women showed more favorable trends regarding the incidence of late-stage BC and BC mortality. A persistent excess of BC incidence, mainly driven by an increase of *in situ* cancers, indicated a moderate amount of overdiagnosis.

There is an ongoing project with the aim to compare BC mortality in screening attenders and nonattenders in Germany, but results of our study are not expected before the end of 2020. Effects of the screening should also be observable in the population context. When an effective mammography screening program is introduced, there are several epidemiological effects to be expected in the screened population. First, BC incidence should show an initial short-term increase (prevalence peak) with the following decline. Second, after several years the incidence of late-stage BC should decline below the level of the prescreening period. Third, BC mortality should decrease in the long term. In broad terms, these effects should be observed mainly in the screened age group while they should not or to a lesser extent occur in the not screened age groups. The aim of our study is to investigate trends in total and stage-specific female BC incidence and BC mortality in screened and not screened age groups before and after the introduction of the German mammography screening program.

Methods**Data and data sources**

The analysis of incidence is based on anonymized individual data of female patients with first (incident) registered ductal carcinoma *in situ* (DCIS, ICD10: D05.1, representing about 95% of all *in situ* BCs) or invasive BC diagnosis (ICD-10: C50). Data on BC cases were retrieved from the German Centre of Cancer Registry Data at the Robert Koch-Institute, Berlin, which collects all cancer data from the population-based cancer registries of the 16 German federal states. We excluded cases only registered on the basis of a death certificate (DCO cases) due to the lack of information on tumor stage and time of diagnosis at initial diagnosis ($n = 18,601$, 5.9% of all invasive BCs). Population data, aggregated by 5 years age groups, was extracted from official population statistics.² Additionally, we retrieved official mortality data for BC (ICD10: C50, cases by 5 years age groups).²

As only anonymized or aggregated data were used, no ethical approval of an ethical review board was required.

Study period and region

The study period for the incidence analyses was set from the year 2003 to the year 2014. The study period was selected by balancing a sufficiently long time-period before the implementation of the mammography screening program with the availability of population-based cancer registry data for a huge,

representative population. The available data enables us to estimate a prescreening incidence for the years 2003/2004, as the first screening units started in late 2005. Most recent data were available for the year 2014, providing a 10-year period after first and a 5-year period after full screening implementation.

We included data from 10 out of 16 federal states into the analysis of incidence. For four federal states (Baden-Württemberg, Berlin, Hesse and Saxony-Anhalt) registration was not present or not complete for the whole study period, for North Rhine-Westphalia only data from the district of Muenster was available. Two further federal states (Bremen and Bavaria) had to be excluded from the analysis due to local statewide screening activities prior to the introduction of the national screening program. Overall, the study region covers a population of 30.8 million inhabitants, representing about 37.7% of the German population.

Data on BC mortality was available all over Germany from 1998 to 2016. Bavaria and Bremen were excluded again for the reason explained above, giving a mean population of 68.8 million inhabitants for mortality analyses.

Information on tumor stage

Stage was defined by cancer registries according to the TNM classification system of the Union for International Cancer Control (UICC) using T- (tumor size), N- (the presence of affected lymph node) and M- (the presence of metastasis) category. These categories allowed generating UICC stage with following categories (statement simplified, for detailed descriptions, see UICC⁵): Stage 0: *in situ* BC, Stage I: tumor ≤ 2 cm, no lymph nodes affected, Stage II: tumor larger than 2 cm but smaller than 5 cm and no lymph nodes affected or tumor smaller than 2 cm and 1–3 lymph nodes affected, Stage III: lymph nodes positive or any size tumor with direct extension, Stage IV: distant metastases present.

Because missing information on stage could substantially bias incidence trends, missing information on stage was treated by multiple imputation.^{6,7} In total, 19.2% of all invasive BC cases had missing data for UICC stage, which was imputed three times by predictive mean matching depending on individual clinical and patient characteristics.

Statistical analysis

For total incidence and mortality, we calculated age-standardized rates using the European standard population (1976). Additionally, we calculated age-specific rates by age

Table 1. Included federal states of Germany for the analysis of incidence, their population (mean 2003–2014) and number of registered DCIS and invasive BC cases (2003–2014), representing 37.7% of the German population

Federal state	Population	DCIS	Invasive BC	Total
Brandenburg	2.51	1,890	22,186	24,076
Hamburg	1.75	1,296	17,865	19,161
Lower Saxony	7.91	6,823	80,504	87,327
Mecklenburg-Western Pomerania	1.66	1,187	14,174	15,361
North Rhine-Westphalia ¹	2.60	2,422	26,101	28,523
Rhineland-Palatinate	4.03	2,996	38,475	41,471
Saarland	1.03	581	10,578	11,159
Saxony	4.18	3,050	38,003	41,053
Schleswig-Holstein	2.82	2,892	31,578	34,470
Thuringia	2.27	1,550	19,568	21,118
Total	30.76	24,687	299,032	323,719

¹data available only for the district of Muenster.

group and UICC stage (for incidence). Six age groups were considered: 50–59 and 60–69 years as screening exposed age groups and 20–39 years, 40–49 years, 70–79 years and 80+ years as nonexposed age groups. The age group younger than 20 years was excluded from age-specific analyses due to small case numbers ($n = 18$, 0.005%, during the total study period). First, we calculated the percentage change of the incidence by dividing mean rates of the most recent 2 years with mammography screening (2013/2014) by mean rates of the two first years (2003/2004), representing baseline incidence, before introduction of the mammography screening. For the analysis of mortality, we compared 2003/2004 to 2015/2016. Second, time trends were calculated by using joinpoint regression models (SEER joinpoint software 4.7.0.0). Joinpoint regression fits piecewise log-linear regression lines to the data and provides estimates of annual percentage changes (APC). A

maximum of two joinpoints was allowed for estimation. Weighted Bayesian Information Criterion (BIC) was used for model selection. Then, 95% confidence limits were provided for the estimations of change and the APCs.

Data availability

Data for BC incidence is available from the German Centre of Cancer Registry Data at the Robert Koch-Institute, Berlin (Scientific Use File, www.krebsdaten.de). Mortality data for BC and population data are available from the Information System of the Federal Health Monitoring (www.gbe-bund.de).

Results

Incidence

A total of 323,719 BC cases (24,687 DCIS (7.6%) and 299,032 (92.4%) invasive BC) were recorded from 2003 to 2014 (Table 1). Age-standardized incidence trends for DCIS, invasive BC and total are shown in Figure 1a. Incidence for invasive BC was 103/100,000 before the introduction of mammography screening (2003/2004), 125/100,000 in the years of full implementation (2008/2009) and 114/100,000 in 2013/2014 (most recent data), giving a 21.6% increase for the typical prevalence peak and a 10.6% increase for the most recent period compared to prescreening incidence. The incidence of DCIS showed an increase of 121.7% from the prescreening period to the peak in 2008/2009 and remained at this level until 2013/2014. Total incidence of BC (DCIS and invasive) increased from 112/100,000 to 134/100,000. Assessing BC incidence within the age groups (Fig. 1b), incidence for invasive BC in the screening age groups was higher in 2013/2014 than before the screening implementation (50–59 years: +7.4%, 60–69 years: +10.4%). Including DCIS the increase was 16.9 and 18.8%, respectively. In the non-screening age groups, a substantial incidence increase was also observed (invasive BC: 20–39 years: +7.5%, 40–49 years: +18.9%, 70–79 years: +10.1%, 80+ years: +9.2%, total incidence including

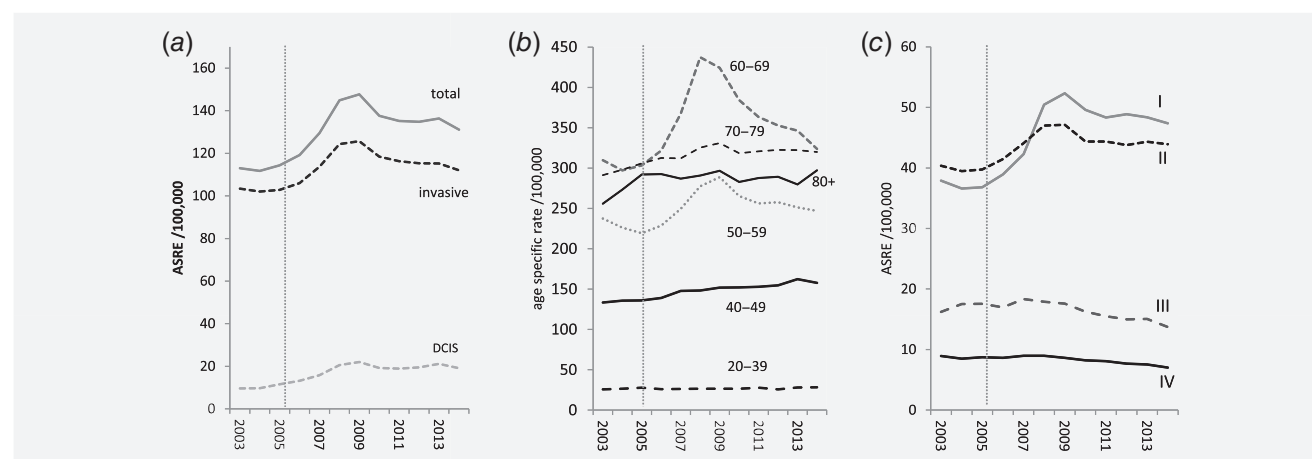


Figure 1. Breast cancer incidence rates per 100,000 women for (a) all age groups (age-standardized), (b) by age (only invasive BC) and (c) by UICC stage (only invasive BC). Vertical dotted line: year of implementation of mammography screening (2005).

DCIS: 20–39 years: +10.4%, 40–49 years: +19.7%, 70–79 years: +11.6%, 80+ years: +9.6%). The relative increase in incidence in age group 40–49 years even exceeded the increase in the screening age groups, but the typical prevalence peak is only visible in the latter. With the implementation of mammography screening, the incidence for stage I and stage II increased until 2008/2009, followed by a decline, but remained higher than the incidence of the prescreening time period (Fig. 1c). Stage III and IV BC incidence was 14.8 and 16.5% lower in 2013/2014 compared to the prescreening values.

Figures 2a–2f displays the stage-specific incidence trends by age groups, Table 2 summarizes the results of joinpoint analyses and the comparison of prescreening and most

recent BC incidence for the selected age groups. In the two youngest age groups (20–39 and 40–49 years, representing 20% of all BCs, Figs. 2a and 2b) no significant trend regarding advanced stage incidence can be observed. However, for age group 40–49 years DCIS, Stage I and II BC incidence showed statistically significant increases by 31.3, 17.7 and 32.4%, respectively. For the screening age groups (Figs. 2c and 2d), comprising 50% of all BC cases, a significant increase of early-stage BC incidence could be observed. The most recent incidence is 156.6%/164.1% higher for DCIS and 31.3%/45.1% for stage I BC compared to prescreening. The incidence of stage II BC showed little change in the screening age groups when comparing data from 2013/2014

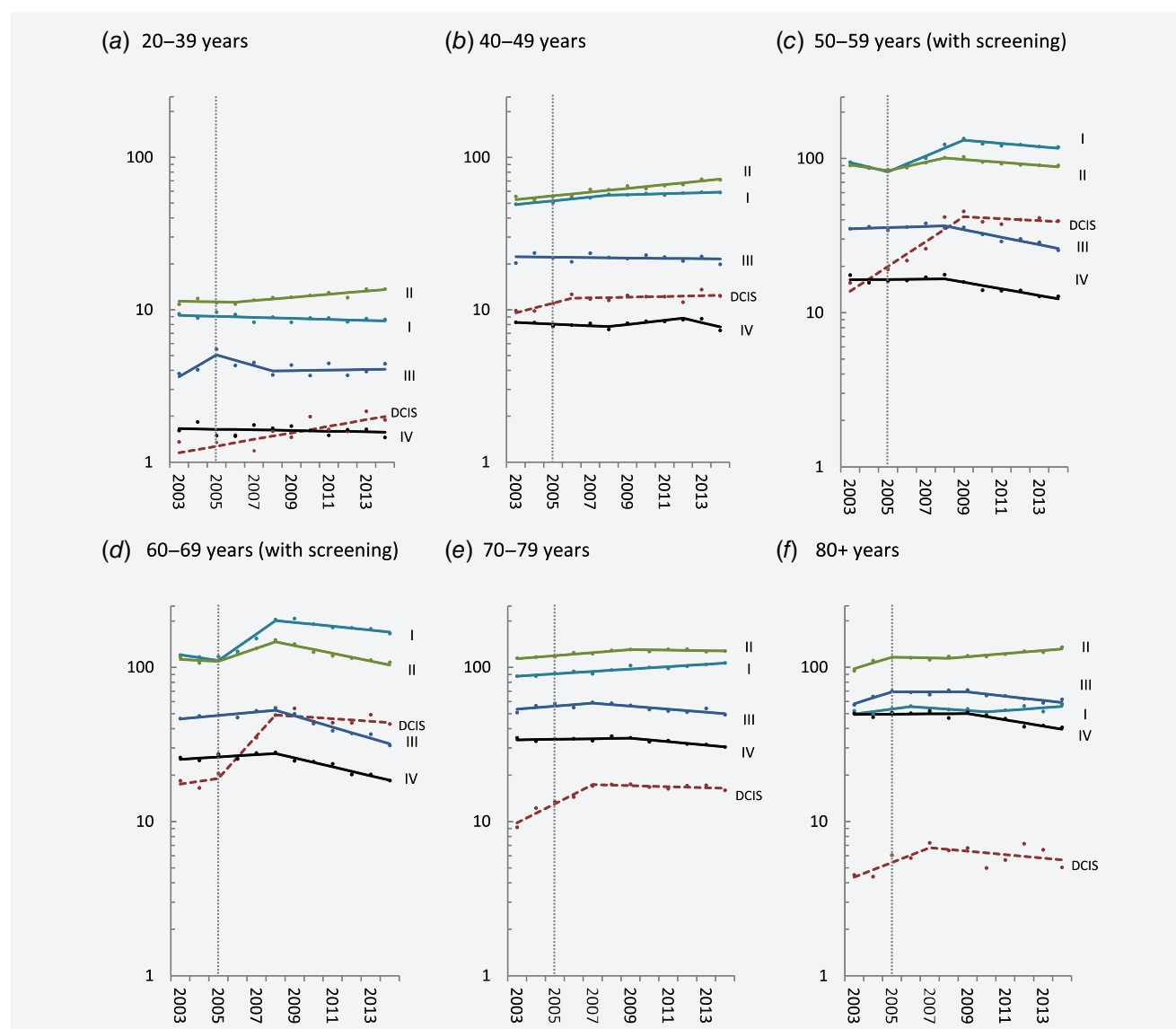


Figure 2. Trends in breast cancer incidence by age group (a–f) and UICC stage in German regions, y-axis: age-specific rates/100,000 women on a logarithmic scale, dots: observed rates, lines: modeled rates by joinpoint regression, vertical dotted line: year of implementation of mammography screening (2005).

Table 2. Breast cancer incidence (rate/100,000) by age group (years) and stage (UICC): comparison of 2003/2004 (before introduction of mammography screening (Mx) in 2005) with 2013/2014 (after introduction, most recent years) and results of trend analyses (joinpoint: year of change in trend, trend as annual percentage change (APC) for given time period), 95% confidence intervals in brackets, significant results in bold

Age group	Stage	Before Mx ¹ /100,000	After Mx ² /100,000	Absolute difference/100,000	Relative difference (%)	Joinpoint	Trend APC (%)
20–39	DCIS	1.1	2.0	0.9 [0.5; 1.3]	76.8 [41.5; 112.0]	–	2003–2014: 5.1 [2.2; 8.1]
	I	9.1	8.7	–0.4 [–1.4; 0.5]	–4.7 [–15.2; 5.9]	–	2003–2014: –0.8 [–1.3; –0.2]
	II	11.3	13.6	2.3 [1.2; 3.4]	20.3 [10.2; 30.3]	2006	2003–2006: –0.5 [–5.2; 4.5] 2006–2014: 2.4 [1.6; 3.2]
	III	3.9	4.2	0.3 [–0.4; 0.9]	6.5 [–10.0; 23.1]	2005 2008	2003–2005: 17.9 [–21.8; 77.7] 2005–2008: –7.8 [–32.3; 25.7] 2008–2014: 0.4 [–2.8; 3.7]
	IV	1.7	1.5	–0.2 [–0.6; 0.2]	–10.2 [–34.5; 14.1]	–	2003–2014: –0.5 [–1.5; 0.5]
40–49	DCIS	9.9	12.9	3.1 [1.7; 4.4]	31.3 [17.6; 45.1]	2006	2003–2006: 7.6 [–1.8; 17.9] 2006–2014: 0.6 [–1.4; 2.6]
	I	50.2	59.1	8.9 [5.9; 11.9]	17.7 [11.8; 23.7]	2008	2003–2008: 2.9 [2.2; 3.6] 2008–2014: 0.7 [0.2; 1.2]
	II	54.1	71.7	17.5 [14.3; 20.8]	32.4 [26.5; 38.3]	–	2003–2014: 2.8 [2.5; 3.2]
	III	21.9	21.1	–0.8 [–2.7; 1.1]	–3.6 [–12.3; 5.1]	–	2003–2014: –0.3 [–0.9; 0.4]
	IV	8.3	8.0	–0.2 [–1.5; 1.0]	–2.9 [–17.9; 12.1]	2008 2012	2003–2008: –1.2 [–2.9; 0.5] 2008–2012: 3.2 [–1.2; 7.8] 2012–2014: –6.4 [–18.4; 7.3]
50–59	DCIS	15.7	40.3	24.6 [22.3; 26.9]	156.6 [141.8; 171.3]	2009	2003–2009: 20.4 [13.4; 27.7] 2009–2014: –1.4 [–8.9; 6.6]
	I	90.7	119.1	28.4 [24.0; 32.8]	31.3 [26.5; 36.2]	2005 2009	2003–2005: –6.7 [–13.4; 0.5] 2005–2009: 12.5 [8.9; 16.3] 2009–2014: –2.4 [–3.7; –1.0]
	II	89.0	90.2	1.2 [–2.8; 5.2]	1.4 [–3.1; 5.9]	2005 2008	2003–2005: –4.2 [–14.5; 7.3] 2005–2008: 6.5 [–4.9; 19.3] 2008–2014: –2.2 [–3.8; –0.5]
	III	35.5	27.0	–8.6 [–10.9; –6.2]	–24.2 [–30.8; –17.5]	2008	2003–2008: 0.9 [–1.7; 3.5] 2008–2014: –5.5 [–7.2; –3.7]
	IV	16.6	12.8	–3.8 [–5.4; –2.2]	–23.0 [–32.8; –13.2]	2008	2003–2008: 0.3 [–2.4; 3.1] 2008–2014: –4.8 [–6.8; –2.9]
60–69	DCIS	17.4	46.1	28.6 [26.2; 31.1]	164.1 [150.0; 178.2]	2005 2008	2003–2005: 4.3 [–26.7; 48.3] 2005–2008: 37.2 [–3.5; 95.1] 2008–2014: –1.9 [–7.6; 4.1]
	I	118.5	171.9	53.5 [45.7; 61.2]	45.1 [38.6; 51.6]	2005 2008	2003–2005: –4.2 [–13.2; 5.6] 2005–2008: 22.1 [10.7; 34.6] 2008–2014: –2.8 [–4.5; –1.1]
	II	111.9	109.7	–2.2 [–2.3; –2.1]	–2.0 [–2.1; –1.8]	2005 2008	2003–2005: –1.5 [–19.3; 20.1] 2005–2008: 10.3 [–7.2; 31.0] 2008–2014: –5.6 [–7.4; –3.8]
	III	47.5	34.1	–13.4 [–14.4; –12.5]	–28.3 [–30.3; –26.3]	2008	2003–2008: 2.6 [–0.0; 5.3] 2008–2014: –8.0 [–9.7; –6.2]
	IV	25.5	19.3	–6.1 [–6.8; –5.5]	–24.2 [–26.6; –21.7]	2008	2003–2008: 1.8 [0.0; 3.5] 2008–2014: –6.5 [–7.6; –5.3]
70–79	DCIS	10.7	16.6	5.9 [4.1; 7.7]	54.7 [37.9; 71.5]	2007	2003–2007: 15.4 [9.4; 21.7] 2007–2014: –0.8 [–3.0; 1.5]
	I	87.7	105.8	18.1 [13.3; 22.8]	20.6 [15.2; 26.0]	–	2003–2014: 1.8 [1.4; 2.2]
	II	115.6	127.0	11.4 [6.1; 16.8]	9.9 [5.3; 14.5]	2009	2003–2009: 2.3 [1.6; 3.0] 2009–2014: –0.4 [–1.3; 0.5]
	III	53.7	51.7	–1.9 [–5.4; 1.6]	–3.6 [–10.1; 2.9]	2007	2003–2007: 2.3 [–1.5; 6.2] 2007–2014: –2.2 [–3.6; –0.8]
	IV	34.1	31.0	–3.1 [–5.8; –0.3]	–9.0 [–17.0; –0.9]	2009	2003–2009: 0.4 [–0.5; 1.3]

(Continues)

Table 2. Breast cancer incidence (rate/100,000) by age group (years) and stage (UICC): comparison of 2003/2004 (before introduction of mammography screening (Mx) in 2005) with 2013/2014 (after introduction, most recent years) and results of trend analyses (joinpoint: year of change in trend, trend as annual percentage change (APC) for given time period), 95% confidence intervals in brackets, significant results in bold (Continued)

Age group	Stage	Before Mx ¹ /100,000	After Mx ² /100,000	Absolute difference/100,000	Relative difference (%)	Joinpoint	Trend APC (%)
80+	DCIS	4.4	5.8	1.4 [0.0; 2.7]	30.5 [−0.7; 61.6]	2007	2009–2014: −2.5 [−3.7; −1.4] 2003–2007: 11.6 [−4.1; 30.0] 2007–2014: −2.6 [−8.6; 3.9]
	I	50.8	54.6	3.8 [−0.5; 8.2]	7.6 [−1.0; 16.1]	2006 2010	2003–2006: 3.7 [−1.9; 9.6] 2006–2010: −1.9 [−6.9; 3.3] 2010–2014: 2.1 [−1.0; 5.3]
	II	102.6	130.2	27.5 [21.0; 34.1]	26.8 [20.4; 33.2]	2005 2008	2003–2005: 9.0 [0.1; 18.8] 2005–2008: −0.5 [−8.1; 7.7] 2008–2014: 2.3 [1.4; 3.3]
	III	60.8	60.4	−0.5 [−4.8; 3.9]	−0.8 [−8.0; 6.5]	2005 2009	2003–2005: 9.3 [−4.8; 25.4] 2005–2009: −0.0 [−5.3; 5.6] 2009–2014: −3.1 [−5.3; −1.0]
	IV	48.8	41.3	−7.5 [−11.6; −3.5]	−15.5 [−23.8; −7.1]	2009	2003–2009: 0.2 [−1.6; 2.1] 2009–2014: −4.6 [−6.9; −2.2]

¹2003/2004.

²2013/2014.

with baseline data. In both age groups joinpoint analysis reveals an increase during the implementation phase of screening (2005–2008), which is superseded by an ongoing declining trend. Stage III and IV incidence only showed a slight initial increase, marginal significant in the case of Stage IV in the oldest age group, followed by a continuing decrease since 2008, by −5.5%/−8.0% per year for Stage III

and −4.8%/−6.5% per year for Stage IV. The incidence in 2013/2014 was reduced by 24.2%/28.3% for Stage III and by 23.0%/24.2% for Stage IV compared to the prescreening period. Trends in the age group of 70–79 years (22% of all BC cases, Fig. 2e) and 80+ years (12% of all BC cases, Fig. 2f) showed increasing incidence for DCIS, Stage I and II, but no typical, screening related prevalence peak. There

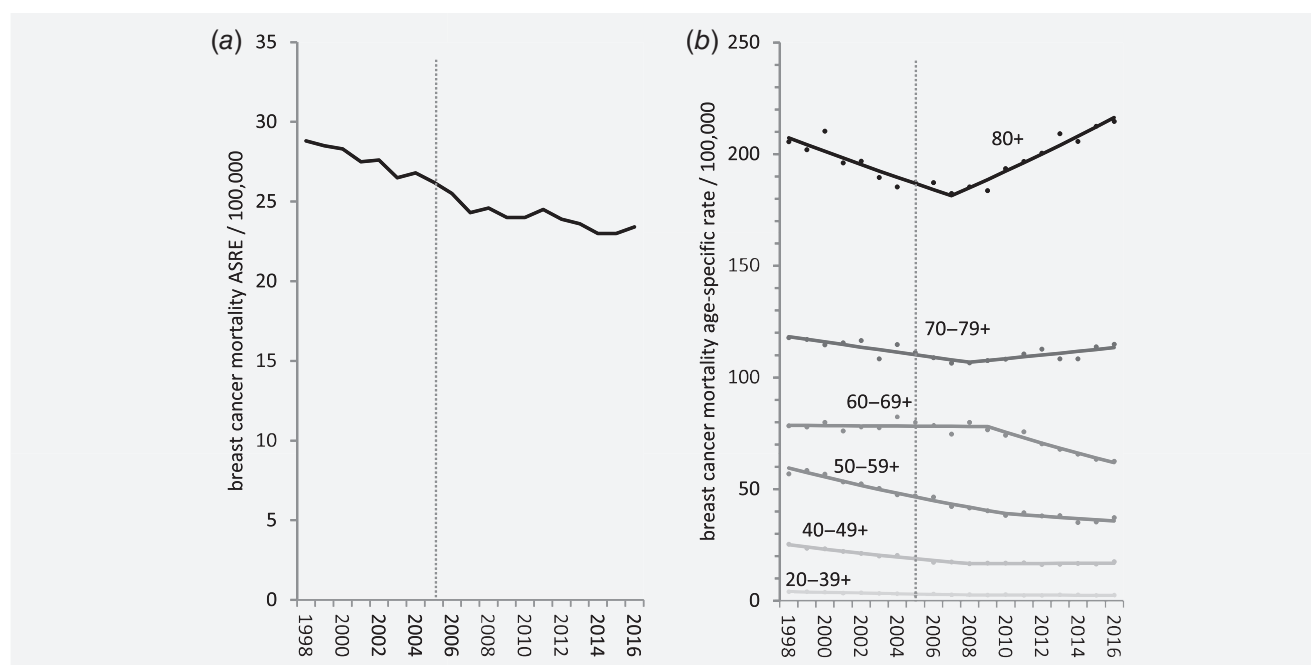


Figure 3. Trends in breast cancer mortality in German regions (a) age-standardized rate (Europe) and (b) age-specific rates/100,000 women, dots: observed rates, lines: modeled by joinpoint regression, vertical dotted line: year of implementation of mammography screening (2005).

Table 3. Breast cancer mortality (age-specific rate/100,000) by age group (years): comparison of 2003/2004 (before introduction of mammography screening in 2005) with 2015/2016 and results of trend analyses 1998–2016 (joinpoint: year of change in trend, trend as annual percentage change (APC) for given time period), 95% confidence intervals in brackets, significant result in bold

Age group	Before Mx ¹ / 100,000	After Mx ² / 100,000	Difference/ 100,000	Difference %	Joinpoint	Trend APC (%)
20–39	3.2	2.4	−0.8 [−1.1; −0.4]	−23.8 [−34.9; −12.6]	2008	1998–2008: −4.3 [−5.5; −3.2] 2008–2016: −0.8 [−2.5; 1.0]
40–49	20.2	17.0	−3.3 [−4.4; −2.1]	−16.1 [−22.0; −10.2]	2008	1998–2008: −4.0 [−4.6; −3.5] 2008–2016: −0.2 [−0.6; 1.0]
50–59	48.9	36.3	−12.6 [−14.5; −10.8]	−25.8 [−29.6; −22.0]	2010	1998–2010: −3.4 [−3.9; −3.0] 2010–2016: −1.5 [−2.9; −0.0]
60–69	79.9	62.9	−16.9 [−19.4; −14.4]	−21.2 [−24.3; −18.0]	2009	1998–2009: −0.1 [−0.6; 0.5] 2008–2016: −3.3 [−4.2; −2.3]
70–79	111.6	114.3	2.8 [−0.8; 6.3]	−2.5 [−0.7; −5.6]	2008	1998–2008: −1.0 [−1.5; −0.5] 2008–2016: 0.7 [0.1; 1.4]
80+	187.5	213.6	26.1 [20.3; 31.9]	13.9 [10.9; 17.0]	2007	1998–2007: −1.5 [−2.0; −1.0] 2007–2016: 2.0 [1.4; 2.5]

¹2003/2004.

²2015/2016.

is a slightly declining trend for Stage III and IV, but markedly smaller than in the screening age groups.

Mortality

A total of 281,284 women died from BC throughout the observation period from 1998 to 2016 in the study population. Age-standardized BC mortality was 26.7/100,000 in the years before the introduction of the mammography program (2003/2004) and 23.2/100,000 in 2015/2016 (relative decrease: −12.9%, Fig. 3a). Trend analyses revealed a decline of BC mortality in almost all age groups until around the years 2008/2009, with the highest decreases in the age groups up to 59 years (Table 3, Fig. 3b). Then trends changed in all age groups. In both younger age groups (20–39 and 40–49 years) mortality remained stable (APC: −0.8% and 0.2%, statistically not significant). In the oldest age groups 70–79 and 80+ years trends reversed with now significantly increasing mortality rates (APC: 0.7 and 2.9%). Only in the screening related age groups still an ongoing significant decrease of BC mortality was observed in the latest time period (APC: 50–59 years: −1.5%; 60–69 years: −3.3%). Compared to the prescreening time period BC mortality in these age groups was −25.8 and −21.2% lower in 2015/2016.

Discussion

The introduction of an organized, high-quality mammography screening in Germany affected trends in breast cancer incidence (total and stage-specific) and in BC mortality. The results are based on a huge population with more than 320,000 BC cases and an underlying population of more than 15 million women, providing robust results for incidence and mortality even in smaller subgroups.

Breast cancer incidence

As expected, our analysis shows an increase in BC incidence in the screening age groups after the introduction of

mammography screening in Germany. The occurrence of a typical prevalence peak, concurrent with full implementation in 2009 and is restricted to screening exposed age groups provides evidence for a causal relationship with the screening intervention. Similar prevalence peaks were also observed in other countries after the introduction of organized mammography screening programs.^{8–11} While the incidence of invasive BC almost fell to the level of the prescreening period about 10 years after the start of the screening program, incidence of DCIS remained substantially elevated since the year of full implementation of the screening (2009). In the long term, an excess of total incidence (*in situ* and invasive carcinomas) after introducing screening might indicate overdiagnosis, that is, cancer cases that would not have been diagnosed in the absence of screening and which represent a much-noticed adverse consequence of mammography screening. Based on a period of 10 years after the start of BC screening program and assuming no underlying secular incidence trends, our results suggest a screening-related excess in total BC incidence of 17–19% in the screening age groups, reflecting a moderate fraction of overdiagnosed BCs. This result is in the range reported from randomized controlled trials or cohort studies (10–22% and 1–36.2%, respectively).¹²

Stage-specific breast cancer incidence

The reduction of advanced BC incidence could be considered as an early surrogate marker for a later reduction of disease-specific mortality.^{13,14} Prognosis of breast cancer depends strongly on the stage of disease at presentation, with significantly lower survival for advanced stages.^{15,16} If a BC screening is effective in reducing the incidence of advanced cancers, by detecting BC before an unfavorable, late-stage is developed, a decline of disease-specific mortality may be expected to follow over the next years. Although one might argue that the decrease in incidence of late-stage cancers is a necessary, but

not sufficient, condition for a screening program to reduce mortality,¹⁷ there is evidence of a causal relationship between these parameters in the case of BC. Based on an analysis of eight RCTs on mammography screening, it has been shown that reductions in the incidence of advanced BC were directly proportional to mortality reductions.¹⁸

In our study, a continuing decline in advanced BC incidence was observed in the screening related age groups (50–69 years). Ten years after the first implementation of the screening program Stage III and IV BC dropped significantly by about a quarter (50–59 years: III: –24.2%, IV: –23.0%; 60–69 years: III: –28.3%, IV: –24.2%). No or substantially smaller changes were seen in the not exposed age groups (20–49 and 80+ years). Opposing effects were observed for early cancer stages with a marked increase in the screening age groups (DCIS: 156.6%, 164.1%; I: 31.3%, 45.1%), while the nonexposed groups showed only minor increases. Especially the increase in DCIS proves that the introduced mammography screening was effective in terms of detecting small breast cancers, because DCIS is rarely discovered by symptoms.^{19,20} All in all, declining advanced stage and increasing early-stage BC incidence in the screening age groups, but not in the others as shown in Figure 2, paint a consistent picture of the expected effects on stage-specific incidence after the introduction of an effective screening program.

One limitation in the interpretation of our result is whether the observed decline of advanced stages can be attributed to the implementation of the mammography screening. In general, incidence trends are not only influenced by screening use, but typically affected by changes in the prevalence of risk factors (e.g., reproductive behavior, use of hormone replacement therapy or obesity). *A priori*, it cannot be ruled out, that changes in some risks might be age-related. Hypothesizing such changes, however, they should have similar effects on all stages and are therefore incapable to explain isolated effects on late-stage BC. Reversely, changes in stage distribution, as they might result from improved diagnostic techniques (e.g., increased use of sentinel lymph node biopsy) should be observable in all age groups; furthermore, they should rather lead to an increase of advanced BC than to a decline.²¹ However, we have no indication that factors mentioned above had substantial impact on BC incidence in the investigated time period. In our case, the decline of advanced BC was isolated to the screening exposed age group making other factors improbable. Therefore, we conclude that even if the evidence level of our observation is limited, a causal relationship between the implementation of the mammography screening program in Germany and the observed stage-specific trends seems likely. A precise estimate of the extent to which screening reduces the incidence of late-stage BC, is not possible due to the observational nature of our data. However, there is good reason to believe that this capacity is stronger than our comparative analysis suggests. To control for incidence trends in the absence of screening we considered BC incidence before the implementation of the screening

program and corresponding trends in nonexposed age groups. Both references, however, are obviously contaminated by opportunistic screening activities. Especially in the screening related age groups, incidences of DCIS at baseline is already high, indicating substantial opportunistic screening use before the start of the program. But also in the adjacent age groups (40–49 years and 70–79 years) incidence of DCIS provides evidence that screening activities took place in 2003/2004 and in the following years. Because of this, our comparisons target also the population effect of quantitative and qualitative improvements in early detection of BC rather than only the effects of screening *versus* no screening. The resulting difficulties with respect to the evaluation of the program had been foreseen already before the start of the program.²⁰ Our results may be limited by the exclusion of DCO cases, in which a higher proportion of late-stage cancers is likely. Sensitivity analyses, which replaced DCO cases by late-stage cancer, showed even stronger declines for advanced stage incidence (due to declining DCO rate over time). In this respect, our results seem to be rather conservative.

A reduction of advanced stages in BC has been found in several studies on mammography screening programs in other regions.^{17,22,23} Some studies, however, did not find such an effect or found only transient drops.^{24,25} A consistent pattern of factors that explain the variance of such study results has not become apparent so far. Methodological differences include the length of the observation period, the definition of advanced BC (UICC or tumor size) and the definition of the age groups compared. These differences often hamper the comparability of publications on stage-specific incidence. An analysis of the Dutch mammography screening, for example, found little impact on the burden of advanced BC. Unlike our approach, all BCs of Stage II and higher had been categorized as advanced BCs.²⁶ Thus, benefits of screening which result from a shift to lower stages within this spectrum are overlooked. Further dilution of possible effects arises from the choice to assign all women at the age of 50 years or older to the exposed age group, although only women until the age of 69, later expanded to 74 were invited for screening. Less favorable results of other studies may also arise from different background incidence trends. An investigation of late-stage BC incidence before and after the introduction of mammography screening in the United States, for example, found only a small decrease by 8% over an observation period of three decades.¹¹ However, the conclusion that screening reduced the incidence of advanced BC only marginally, critically depends on the assumption of a constant underlying disease burden. This condition is questionable. Early incidence trends in the screening age group (1976–1985) show a clear increase of late-stage BC. With the introduction of mammography screening this trend was stopped. Without screening it could be assumed that late-stage BC would have increased further on. Therefore, the reported decrease of 8% in our study might be a rather relevant effect.

Even if there is no totally clear picture of declining late-stage BC incidence after introduction of mammography screening in the literature, our result, which are based on a strict stratification of screening exposure and exact stage, suppose a beneficial effect of mammography screening on late-stage BC incidence.

Breast cancer mortality

The ultimate goal of mammography screening is a reduction of BC mortality. The proof of this effect on the population level is a big challenge because trends in mortality are influenced not only by changes in the disease but also by improvements in treatment. In Germany, a constant decline in BC mortality was already seen in all age groups before the introduction of the mammography screening in 2005. This trend might reflect the ongoing advances in BC therapy. When an effective BC screening is introduced, one would expect that the decline in BC mortality would be strengthened, mainly in the screening age group. Interestingly the declining trend in BC mortality stopped around the year 2008/2009 in the nonexposed age groups, whereas even a significant increase was observed for patients aged 70 and older. Only in the screening exposed age groups still favorable trends are present with an annual percentage decline of -1.5% (50–59 years, starting 2010) and -3.3% (60–69 years, starting 2009). Both screening age groups also show the largest absolute reduction in BC mortality. This is in line with results from RCTs that suggest effects on mortality to appear at about 4 years after the first screenings and to fully emerge after about 10 years.²⁷ Other population-based studies also found a close temporal connection between the implementation of a mammography screening and trend changes in mortality.^{28–31} We have to take into account the possibility that effects on mortality were accelerated by an increase of breast cancer awareness and opportunistic screening in the run-up to the program.

Summarizing the results, we conclude that the observed trend changes in BC mortality, with continuing decline in the screening exposed group and not in the nonexposed groups, fit very well to expected effects of an effective mammography screening. It remains unclear to what extent the screening contributed to the reduction in BC mortality. Further analyses are needed here.

Attendance rate

The attendance rate to the German mammography screening is about 50%. Compared to other European programs, achieving attendance rates of 70% and more,^{29,32,33} screening uptake in the official German program seems to be relatively low. The question arises as to whether the observed results in our study are consistent with this moderate participation rate. Would the effects, mortality decline as well as the proportion of overdiagnosis, intensify if participation in the program increased? This seems to be unlikely. Unfortunately, the German health care system opens different ways of getting screening mammography outside the official screening program (opportunistic screening). The results of a recent survey showed that 73% of women in the screening age group had a mammography in the last 2 years (83% for “ever” had a mammogram)³⁴ which is in compliance with earlier surveys.^{35,36} Insofar a realistic screening rate for Germany might be clearly higher than 50%, likely about 70% and comparable to other European countries. Such an attendance rate could explain the extent of the observed population-based effects on late-stage BC, overdiagnosis and mortality as well.

Limitations

A limitation of our study results from its relatively short observation period, but more recent data is not available. The lack of long-term data on incidence before the screening program impedes a more in-depth consideration of background trends beyond comparison of different age groups alone. Availability of more recent data, on the other hand, might reveal delayed effects, particularly with respect to disease-specific mortality.

Conclusions

The observed reduction of late-stage breast cancer incidence in the screening exposed age group in Germany is most likely to be attributed to the introduction of the national mammography screening program. In addition, the observed reduction of disease-specific mortality fits the expected pattern, but the proportion to which the mammography screening contributed to the reduction is unclear. These positive effects are bought at the cost of a moderate occurrence of overdiagnosis, especially by a sharp increase of *in situ* cancers.

References

1. Robert Koch-Institut. *Cancer in Germany 2013/2014*. Berlin: Robert Koch-Institut, 2018.
2. GBE. Gesundheitsberichterstattung des Bundes—The Information System of the Federal Health Monitoring. Available from: www.gbe-bund.de. Accessed 13 June 2019, 2019.
3. Perry N, Broeders M, de Wolf C, et al. *European guidelines for quality assurance in breast cancer screening and diagnosis*, 4th edn. Brussels, Belgium: European Communities, 2006.
4. Malek D, Käb-Sanyal V. Implementation of the German Mammography Screening Program (German MSP) and First Results for Initial Examinations, 2005–2009. *Breast Care* 2016; 11:5.
5. Sobin LH, Gospodarowicz M, Wittekind C. *TNM Classification of Malignant Tumours*, 7th edn. Hoboken, NJ: Wiley-Blackwell, 2011. 336.
6. Eisemann N, Waldmann A, Katalinic A. Imputation of missing values of tumour stage in population-based cancer registration. *BMC Med Res Methodol* 2011;11:129.
7. van Buuren S, Groothuis-Oudshoorn K. MICE: Multivariate Imputation by Chained Equations in R. *J Stat Softw* 2011;45:1–67.
8. Hofvind S, Sorum R, Thoresen S. Incidence and tumor characteristics of breast cancer diagnosed before and after implementation of a population-based screening-program. *Acta Oncol* 2008;47: 225–31.

9. Jorgensen KJ, Gotzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. *BMJ* 2009;339:b2587.
10. Pollan M, Michelena MJ, Ardanaz E, et al. Breast cancer incidence in Spain before, during and after the implementation of screening programmes. *Ann Oncol* 2010;21(Suppl 3):iii97–102.
11. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med* 2012;367:1998–2005.
12. Carter JL, Coletti RJ, Harris RP. Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. *BMJ* 2015;350:g7773.
13. Jonsson H, Johansson R, Lennar P. Increased incidence of invasive breast cancer after the introduction of service screening with mammography in Sweden. *Int J Cancer* 2005;117:842–7.
14. Mandrik O, Zielonke N, Meheus F, et al. Systematic reviews as a 'lens of evidence': Determinants of benefits and harms of breast cancer screening. *Int J Cancer* 2019;145:994–1006.
15. Svendsen AL, Olsen AH, von Euler-Chelpin M, et al. Breast cancer incidence after the introduction of mammography screening: what should be expected? *Cancer* 2006;106:1883–90.
16. Walters S, Maringe C, Butler J, et al. Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000–2007: a population-based study. *Br J Cancer* 2013;108:1195–208.
17. Welch HG, Prorok PC, O'Malley AJ, et al. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. *N Engl J Med* 2016;375:1438–47.
18. Autier P, Hery C, Haukka J, et al. Advanced breast cancer and breast cancer mortality in randomized controlled trials on mammography screening. *J Clin Oncol* 2009;27:5919–23.
19. Paci E, Duffy S. Overdiagnosis and overtreatment of breast cancer: overdiagnosis and overtreatment in service screening. *Breast Cancer Res* 2005;7:266–70.
20. Giersiepen K, Haartje U, Hentschel S, et al. Brustkrebsregistrierung in Deutschland: Tumorstadienverteilung in der Zielgruppe für das Mammographie-Screening. *Dtsch Arztebl* 2004;101:6.
21. Maaskant AJ, van de Poll-Franse LV, Voogd AC, et al. Stage migration due to introduction of the sentinel node procedure: a population-based study. *Breast Cancer Res Treat* 2009;113:173–9.
22. Harding C, Pompei F, Burmistrov D, et al. Breast cancer screening, incidence, and mortality across US Counties. *JAMA Intern Med* 2015;175:1483–9.
23. Fracheboud J, Otto SJ, van Dijk JA, et al. Decreased rates of advanced breast cancer due to mammography screening in The Netherlands. *Br J Cancer* 2004;91:861–7.
24. Autier P, Boniol M, Middleton R, et al. Advanced breast cancer incidence following population-based mammographic screening. *Ann Oncol* 2011;22:1726–35.
25. Jacklyn G, McGeechan K, Irwig L, et al. Trends in stage-specific breast cancer incidence in New South Wales, Australia: insights into the effects of 25 years of screening mammography. *Breast Cancer Res Treat* 2017;166:843–54.
26. Autier P, Boniol M, Koechlin A, et al. Effectiveness of and overdiagnosis from mammography screening in The Netherlands: population based study. *BMJ* 2017;359:j5224.
27. Nystrom L, Andersson I, Bjurstam N, et al. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet* 2002;359:909–19.
28. Blanks RG, Moss SM, McGahan CE, et al. Effect of NHS breast screening programme on mortality from breast cancer in England and Wales, 1990–8: comparison of observed with predicted mortality. *BMJ* 2000;321:665–9.
29. Haukka J, Byrnes G, Boniol M, et al. Trends in breast cancer mortality in Sweden before and after implementation of mammography screening. *PLoS One* 2011;6:e22422.
30. Otto SJ, Fracheboud J, Looman CW, et al. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. *Lancet* 2003;361:1411–7.
31. Sankatsing VDV, van Ravesteyn NT, Heijnsdijk EAM, et al. The effect of population-based mammography screening in Dutch municipalities on breast cancer mortality: 20 years of follow-up. *Int J Cancer* 2017;141:671–7.
32. Otten JD, Broeders MJ, Fracheboud J, et al. Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality, 1975–2006. *Int J Cancer* 2008;123:1929–34.
33. Hofvind S, Lee CL, Elmore JG. Stage-specific breast cancer incidence rates among participants and non-participants of a population-based mammographic screening program. *Breast Cancer Res Treat* 2012;135:291–9.
34. Schmucker C, Zok K. Informierte Teilnahme an Früherkennungsuntersuchungen: Ergebnisse einer Befragung unter GKV-Versicherten. In: Günster C, Klauber J, Robra B-P, Schmacke N, Schmucker C. *Versorgungsreport Früherkennung*. Medizinisch Wissenschaftlichen Verlagsgesellschaft Berlin, 2019:31–78.
35. Starker A, Sass AC. Participation in cancer screening in Germany: results of the German Health Interview and Examination Survey for Adults (DEGS1). *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2013;56:858–67.
36. Starker A, Buttman-Schweiger N, Krause L, et al. Cancer screening in Germany: availability and participation. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2018;61:1491–9.